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**EP 0 189 612 B1**

COLLECTION OF THE CZECHOSLOV.CHEMICAL COMMUNICATIONS, vol. 40, no. 5, May 1975, pages 1612-1622, PRAGUE, CS; I.CERVENA et al: "Naphthylpiperazines and tetralylpiperazines: Synthesis and pharmacological properties"

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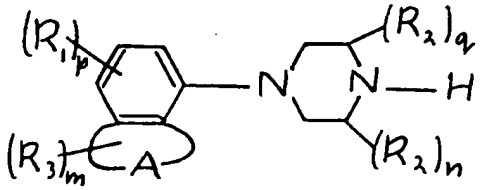
## Description

The invention relates to new pharmaceutical compositions having a psychotropic activity, to new piperazine derivatives which may be used in such compositions as the active substance, and to the preparation of the said compositions and active compounds.

It was found that compounds of the general formula 1

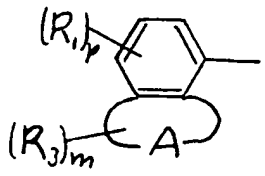


(1)

wherein

- $-R_1$ is alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, alkylthio, nitro, amino, mono- or dialkylamino, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxyl, and p has the value 0-3;
- $-R_2$ is an alkyl group and n and q can have the value 0 or 1;
- $-R_3$ may have the same meanings as $R_1$, or is benzoyloxymethyl or methylidene ,an oxo or thioxogroup, and m has the value 0-2;
- -A forms, with the two carbon atoms of the phenyl group, a saturated or fully or partly unsaturated cyclic group having 5-7 atoms in the ring, which comprises 1-3 hetero atoms from the group O, S and N, with the proviso that the sum of the number of oxygen and sulphur atoms is at most 2,

and exclusive of those compounds wherein n and q are 0, and A together with the two carbon atoms of the phenyl group forms a heterocyclic group having 5 or 6 ring atoms which as the only hetero atom contains a nitrogen atom on the meta position in relation to the piperazine group, and exclusive of compounds of general formula 1, wherein the group of general formula 2



(2)

is a 4-(or 7-)benzimidazolyl group which may be substituted in position 2 with alkyl, or a 7-indolyl group, or a 4- (or 7-) benzotriazolyl group, or a 5- (or 8-) carbo (or 3,4-dihydrocarbo)-styryl group, or a 8-quinolinyl group, and the acid addition salts of these compounds have interesting psychotropic properties.

As a halogen atom, $R_1$ is preferably fluoro, chloro or bromo, and as an alkyl group, for example, a straight or branched, saturated or unsaturated group having 1-5 carbon atoms.

When $R_2$ is an alkyl group, this is preferably the methyl group or ethyl group.

As a hydroxyalkyl group, the group $R_3$ preferably comprises 1-3 carbon atoms.

Compounds which are preferred on the basis of their activity pattern are:

a) 1-[5-(1,4-benzodioxanyl)] piperazine,
b) 1-[8-(1,3-benzodioxanyl)] piperazine,
c) 1-[7-(benzofuranyl)] piperazine,
d) 1-[4-(1,3-benzodioxolyl)] piperazine,
e) 1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine,
f) 1-[7-(5-fluorobenzofuranyl)] piperazine,
g) 1-[8-(1,2,3,4-tetrahydroquinolyl)]piperazine,
h) 1-[8-(2-oxo-1-benzopyranyl)]piperazine,
i) 1-[8-(2H-1-benzopyranyl)]piperazine,
j) 1-[5-(2-methyl-1,4-benzodioxanyl)]piperazine,
k) 1-[7-(4-fluorobenzofuranyl)]piperazine,
l) 1-[8-(isoquinolyl)]piperazine,

m) 1-[7-(4-bromobenzofuranyl)]piperazine,
n) (+)-1-[5-(2-methoxymethyl-1,4-benzodioxanyl)]piperazine,
o) 1-[7-(4-methylbenzofuranyl)]piperazine,
p) 1-[7-(4-chlorobenzofuranyl)]piperazine,
q) 1-[7-(5-chlorobenzofuranyl)]piperazine.

When a chiral carbon atom is present, both the racemate and the individual isomers belong to the invention.

Suitable acids with which the compounds of general formula 1 can form pharmaceutically acceptable acid additon salts are, for example, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluenesulphonic acid, methanesulphonic acid, and naphtalenesulphonic acid.

The above-described compounds of general formula 1 have a psychotropic activity and are hence excellently suitable for the treatment of affections or diseases which are the result of disturbances in the central nervous system, for example, psychoses, aggression, fear and depression. Some of the compounds moreover have also a good central analgetic activity.

Dependent on the meanings of the symbols A, $R_1$-$R_3$, m, n, p and q some compounds of the general formula 1 have a strong thrombolytic activity. This property makes these compounds particularly suitable for use in the treatment of hematological disorders.

An important advantage of the present compounds of general formula 1 is that their activity is very specific. It was found, for example, that in mice the antiaggressive activity is not associated with undesired sedative effects.

As a rule the antipsychotic activity is produced without the side effects, which are generally considered to be undesired, as a result of dopaminolytic and sedative activity.

Dependent on the meanings of the groups A and $R_1$-$R_3$, both the antiaggressive activity and the antipsychotic activity may be most prominent.

The antiaggressive activity of the compounds was measured in a test suitable for that purpose on isolated mice [Advances in Pharmacol. 5, (1967), 79]. In this test, male albino mice were kept isolated for a period of 4 weeks and were then selected for the test on the basis of fighting behaviour present. The selection criterion is the occurrence of 3 or more fighting periods within 3 minutes after a mouse which had not been kept isolated is placed in the cage of the mouse which had been kept isolated.

The compounds to be investigated were administered orally to the selected mice. Five mice per dose were used. Sixty minutes after administration of the compound to be investigated, the animals were again evaluated for fighting behaviour. The compound to be investigated is inactive in the administered dose when in this case also 3 or more fighting periods were observed within 3 minutes after a mouse which had not been kept isolated was placed in the cage of the mouse which had been kept isolated. The $ED_{50}$-value in mg of active substance per kg of body weight was calculated form the results obtained.

The compounds according to the invention have an $ED_{50}$-value which is smaller than 20 mg/kg and for most of the compounds the $ED_{50}$-value is 0.1-5 mg/kg.

Due to the strong antiaggressive activity and the absence of undesired side effects, for example, sympatholytic, dopaminolytic, muscle relaxing and sedative properties, the compounds are excellently suitable for use in the treatment of intra- and extrapunitive behaviour and overt aggressive behaviour in man and animal.

For use in humane medicine are to be considered first of all the control of aggressive symptoms in psychiatric diseases and serious forms of psychopathological aggression.

As application possibilities in the veterinary field are to be considered especially those forms of aggression which occur in the transport of agricultural domestic animals and the mixing of groups of these animals.

The antipsychotic activity of the compounds of general formula 1 was determined in a test procedure in which the suppression of conditioned behaviour in test animals was measured according to procedures known per se. The compounds are considered to be active if they show at least a suppression of 50% of the conditioned behaviour after oral administration in dosages of 50 mg/kg or less. The dopaminolytic activity of these compounds can be determined according to known behavioural or biochemical tests, for example, induction of catalepsy, increasing of the dopamine synthesis or conversion rate in the central nervous system, and by the affinity to dopamine receptors which is determined by displacement of a radioactive labelled ligand in a tissue homogenate.

The sedative activity of these compounds was studied in a test in which the influencing of the spontaneous locomotoric activity of test animals is measured according to known methods.

For the active compounds of general formula 1 it was found that generally dopaminolytic and sedative

effects do not occur in dosages which are at least a factor three higher than the dosages which give 50% suppression of the conditioned behaviour.

The quantity, frequency and way of administration may differ for each individual case, also dependent on the nature and the severity of the disturbances. A dosage of 5-500 mg and preferably of 25-150 mg daily are generally suitable for humane application.

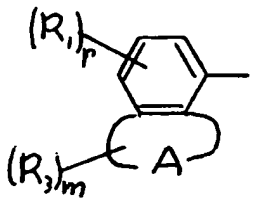
For veterinary purposes the dosage preferably is 0.1-10 mg/kg of body weight.

The analgetic activity of the compounds was determined in an analgetic test in mice [Brit. J. Pharm. 9, (1954), 280]. In this test the pain stimulus was generated by placing bulldog clips on the tailhead of a mouse. The animals try to remove the pain stimulus by biting. The non-occurence of the pain response after administration of test substances is a measure of the analgetic activity. The compounds to be tested were administered orally. Five mice were used per dose. Sixty minutes after the administration of the compounds to be tested, the occurrence of the pain response was established. From the results obtained the $ED_{50}$-values in mg/kg of active substance per kg of body weight were calculated.

The thrombolytic activity is determined using the method described by Kumada et al [Thrombosis Research, 18, (1980), 189-203].

The active compounds according to the invention and their acid addition salts can be processed, according to known standard methods, to compositions such as pills, tablets, coated tablets, capsules, powders, injection liquids, and the like while using the conventional auxiliary substances, for example, solid and liquid carrier materials.

The compounds of general formula 1 are new compounds with the exception of the compounds wherein n and q are 0, and A together with the two carbon atoms of the phenyl group forms a heterocyclic group having 5 or 6 ringatoms, which as the only hetero atom contains one nitrogen atom at the meta position in relation to the piperazine group (some of these compounds are known from French patent specification 81.23744), and compounds in which n and q are 0, and the group of general formula 2

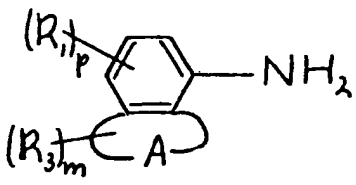


(2)

is a 4-(or 7-)benzimidazolyl group which may be substituted in position 2 with alkyl, or a 7- indolyl group, or a 4-(or 7-)benzotriazolyl group (which compounds are known from Netherlands Patent Application 82.01708), or a 5-(or 8-)carbo (or 3,4-dihydrocarbo-)styryl group (which compounds are known from Netherlands patent application 81.04923), or an 8-quinolinyl group [which compound is known from Ber. 74B, (1941), pp. 1661-1663].

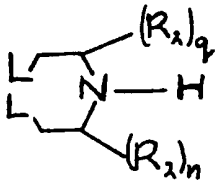
The new compounds according to the invention can be prepared in a manner known for the synthesis of analogous compounds [see, for example, United States Patent Specification 2,976,290 and J.Med.Chem. 8, (1965), pp. 104-107].

The compounds can be obtained, for example, by reaction of a compound of general formula 3



(3)

with a compound of general formula 4,



(4)

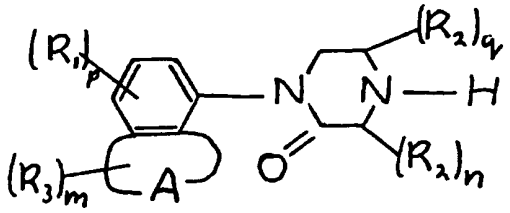
in which formula L is a so-called leaving group, preferably chlorine, bromine, alkyl-$SO_3$ or aryl-$SO_3$.

This reaction may be carried out both in an inert apolar organic solvent, and in a protic polar solvent. Examples of suitable solvents are chlorobenzene, toluene, pyridine, acetonitrile, lower aliphatic alcohols, for example, ethanol, propanol and butanol. In order to bind the releasing acid, an acid binder, for example $NaHCO_3$ or $K_2CO_3$ or an organic base, for example, triethylamine, may be used.

The reaction temperature usually is between room temperature and the boiling-point of the solvent used.

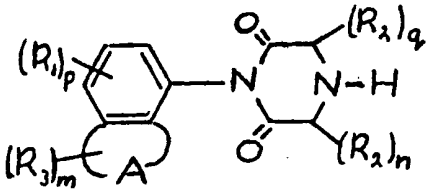
It is sometimes necessary or desired in this mode of preparation first to replace the hydrogen atom at the nitrogen atom in the starting material of general formula 4 by a protective group, for example, the benzyl group, an aryloxycarbonyl group or alkoxycarbonyl group the alkoxy group of which comprises 1-4 C-atoms. Said protective group can then be removed from the resulting final product by means of the methods conventionally used for this purpose, for example, by catalytic hydrogenation or by acid hydrolysis. Conventional solvents are lower aliphatic alcohols and aliphatic esters thereof or aqueous mineral acid. The reactions are carried out at temperatures between room temperature and reflux temperature of the solvent used.

The compounds of general formula 1 can furthermore be obtained by reduction of a compound of general formula 5



(5)

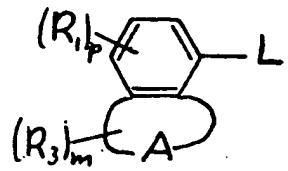
or general formula 6,



(6)

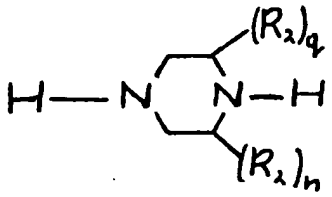
in which the symbols have the above-mentioned meanings. This reduction reaction may be carried out, for example, with suitable reduction agents, for example $LiAlH_4$ or a $BH_3.S(CH_3)_2$-complex in a suitable solvent, for example, ether or tetrahydrofuran. The reaction is carried out at temperatures between room temperature and the reflux temperature of the solvent used. This method can be used readily only when besides the keto group or keto groups to be reduced, no other groups sensitive to reduction are present in the starting substances of general formula 5 or 6.

Another suitable method of preparing the compounds of general formula 1 is the reaction of a compound of general formula 7



(7)

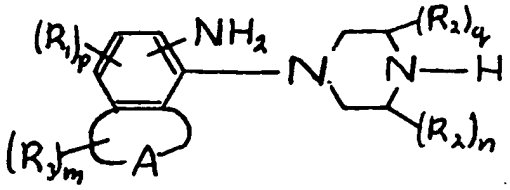
with a piperazine of general formula 8,



(8)

in which A, $R_1$-$R_3$, p, n, q and m have the above-mentioned meanings and L is a leaving group, for example, a halogen atom or nitro group. This reaction is carried out in a suitable organic solvent, for example, toluene, xylene, or a mono- or polyalcohol of higher boiling-point, at the reflux temperature of the solvent used.

The compounds of general formula 1 can further be prepared by reaction of a compound of general formula 9



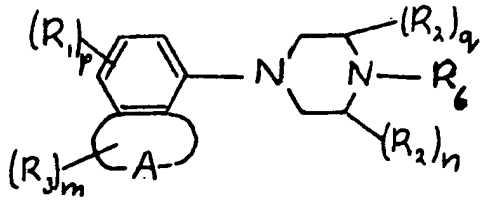
(9)

with $NaNO_2$ in the manner described, inter alia, in J.Chem.Soc. 1971, 3994-3999 in a sulphuric acid or hydrochloric acid medium, in which the resulting diazonium salt is decomposed with, for example, 50% hypophosphoric acid. The reaction is carried out at temperatures between 0° C and room temperature.

Some compounds of general formula 1 can furthermore be obtained by conversion of another compound of general formula 1. For example, compounds of general formula 1, in which $R_1$ and/or $R_3$ is/are an esterified hydroxyl function, can be converted by hydrolysis via a method known per se into compounds in which $R_1$ and/or $R_3$ is/are hydroxyl.

Another possibility is to saturate or introduce a double bond in compounds of general formula 1, by hydrogenation or dehydrogenation, dependent on the structure.

Moreover, compounds of the general formula 1, wherein n and/or q has the value 1 can be obtained by introducing one or two groups $R_2$ starting with the corresponding compounds of the general formula 1 wherein n and/or q has the value 0. According to this process [Chem. Rev. 78, (1978), 275 and 84, (1984), 471] a compound of the general formula 1 is converted into a compound of the general formula 10

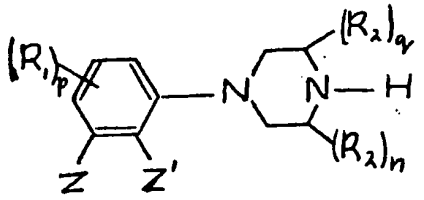


(10)

wherein $R_1$-$R_3$, m, n, p and q have the above meanings, and $R_5$ is an activating group, for example a nitroso group. Then the compound of general formula 10 is alkylated with a compound $R_2$-L, wherein $R_2$ and L have the above meanings. After the alkylation the activating group $R_5$ is removed in a way known per se, whereby the desired compound of general formula 1 is obtained.

The reaction is carried out in a suitable organic solvent such as for example a lower alkane, diethyl ether or tetrahydrofuran, in the presence of a strong base, for example aryl- or alkyllithium or a lithium dialkylamine, at temperatures preferably between -100 °C and 0 °C.

Finally, compounds of general formula 1 can be obtained, dependent on the meaning of A, by converting compounds of general formula 11



(11)

into compounds of general formula 1 by a cyclisation reaction. This cyclisation generally takes place, dependent on the meanings of Z and Z' and the desired meaning of A, via methods known per se for this type of substances or analogous thereto.

The starting materials to be used in the above-described methods can be obtained, in so far as these are new compounds, in a manner known for the synthesis of analogous compounds.

The invention will be further described with reference to the ensuing specific examples.

EXAMPLE I

1-[5-(1,4-benzodioxanyl)] piperazine, hydrochloride.

128 Mmol (23.9 g) of 5-amino-1,4-benzodioxan and 140 mmol (25.0 g) of bis-(2-chloroethyl)amine HCl were suspended in 250 ml of chlorobenzene. The mixture was heated at 130 °C for 66 hours while stirring. The reaction mixture was cooled to 90 °C and diluted with 200 ml of ethyl acetate. The solid was filtered off and washed with ethyl acetate. The crude substance was recrystallized from ethanol and the title compound was obtained having a melting-point of 256-258° C.

EXAMPLE II

1-[8-(1,3-benzodioxanyl)] piperazine, hydrochloride.

18.7 Mmol (5.8 g) of 1-[8-(1,3-benzodioxanyl)] -4-benzylpiperazine were dissolved in 150 ml of 96% ethanol after which 1 g of 10% palladium on carbon was added. The mixture was then hydrated at 50° C with 450 ml of hydrogen. The reaction mixture was filtered over hyflo and the filtrate was evaporated to dryness under reduced pressure.

The evaporation residue was dissolved in 100% ethanol and 1 equivalent of hydrochloric acid in ethanol was added hereto. The solution was treated with carbon and after filtration over hyflo the filtrate was diluted with ether. The title compound was isolated with a melting-point of 217-219° C. EXAMPLE III

1-[5-(1,4-benzodioxanyl)] -3-methylpiperazine, hydrochloride.

64 Mmol (16,7 g) of 1-[5-(1,4-benzodioxanyl)] -3-methylpiperazine-2,6-dione were dissolved under an atmosphere of nitrogen in 200 ml of tetrahydrofuran distilled over lithium aluminium hydride.

170 Mmol (12.9 g) of borane-dimethyl sulphide complex (16.3 ml) were carefully added to this solution, after which the whole was heated slowly to 40° C. During the moderately exotherm reaction, a mixture of dimethylsulphide and tetrahydrofuran was distilled off, the total volume of the reaction mixture being kept constant by simultaneously adding dropwise tetrahydrofuran. After 300 ml of distillate had been collected, the reaction mixture, in which a precipitate had formed, was cooled to -10° C. At this temperature, 80 ml of 6 N hydrochloric acid were added dropwise, after which the reaction mixture, without a cooling bath, slowly reached room temperature. After leaving to stand for 16 hours, the mixture was heated to reflux in which a bright solution was formed and tetrahydrofuran was distilled off. While cooling with ice, 270 ml of 2 N sodium hydroxide were added to this solution, after which the mixture was extracted with 3 x 300 ml of ethyl acetate. The organic layer was washed with water and then dried on sodium sulphate and evaporated

to dryness in vacuo. The residue after evaporation was dissolved in a mixture of ethyl acetate-ethanol and 1 equivalent of hydrochloric acid in ethanol was added hereto, after which the title compound was obtained with a melting-point of 220-224° C.

EXAMPLE IV

5-(1-piperazinyl)quinoxalin, hydrochloride.

0.2 Mol (33.5 g) of 5-chloroquinoxalin and 2.1 mol (184 g) of piperazine were mixed in 180 ml of ethylene glycol and refluxed for 20 hours.
The reaction mixture was poured on ice and acidified with concentrated hydrochloric acid and then extracted with 3 x 200 ml of ether. The water layer was made alkaline while cooling with ice, with 50% sodium hydroxide and then extracted with 3 x 600 ml of methylene chloride. The combined methylene chloride solution was washed successively with 1 l of 1N sodium hydroxide and a mixture of 925 ml of a saturated saline solution and 75 ml of 50% potassium hydroxide. The organic solution was dried on sodium sulphate and was then evaporated to dryness in vacuo. The residue was chromatographed over silica gel with a mixture of methylene chloride, methanol, and 25% ammonia (92 : 7.5 : 0.5) as eluent. The resulting free base was dissolved in ethanol and 1 equivalent of hydrochloric acid in ethanol was added. The title compound was obtained with a melting-point of 271-272° C.

EXAMPLE V

1-[5-(2-hydroxymethyl-1,4-benzodioxanyl)] piperazine, dihydrochloride.

6,6 Mmol of 1-[5-(2-benzoyloxymethyl-1,4-benzodioxanyl)]piperazine were suspended in 100 ml of ethanol, after which a solution of 0.95 g of 85% KOH in 10 ml of water was added in one portion. After stirring at room temperature for 2.5 hours, the suspension was concentrated by evaporation at reduced pressure. The residue was then extracted with chloroform. The residue obtained after evaporation was finally converted with 2 equivalents of hydrochloric acid into the dihydrochloride of the title compound with a melting-point of 228-233° C.

EXAMPLE VI

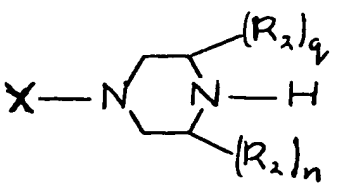
1-[8-(1,2,3,4-tetrahydroquinolinyl)] piperazine, dihydrochloride.

7.5 g Of $NiCl_2.6H_2O$ were added while stirring at 10-15° C to 10.5 mmol of 1-(8-quinolinyl) piperazine in 75 ml of methanol. 11.9 g Of $NaBH_4$ were then added in portions in approximately 30 hours at 10-20° C. The reaction mixture was worked up by pouring in a mixture of 70 ml of water and 30 ml of concentrated hydrochloric acid. After heating at 90° C for 20 minutes, the mixture was cooled and 20 ml of 50% NaOH solution was added. The title compound was finally obtained by extraction with chloroform and a chromatographic purification over silica gel, succeeded by the preparation of the dihydrochloride with 2 equivalents of hydrochloric acid in ethanol. Melting-point 330-334° C.

EXAMPLE VII

1-[4-(3-methyl-1,2-benzisoxazolyl)] piperazine, fumarate.

86.9 Mmol of 1-(3-fluoro-2-acetyloxim-phenyl) piperazine were dissolved in 100 ml of DMSO, after which 6.7 g of 85% KOH were added. The mixture was poured in 500 ml of water, while stirring, and extracted with 3 x 300 ml of ethyl acetate. The product obtained after drying on magnesium sulphate and evaporation was dissolved in hot ethanol, after which 1 equivalent of fumaric acid was added in 150 ml of hot ethanol.
The title compound was sucked off after crystallization and had a melting-point of 216-219° C.
Analogously to the methods described in the Examples I to VII, the compounds of general formula 12



(12)

recorded in the table below were prepared according to the method of the specific example also mentioned in the table:

TABLE

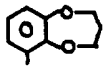
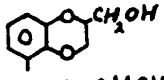
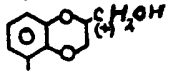
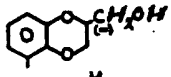
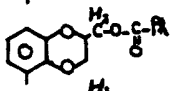
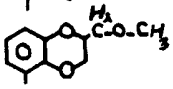
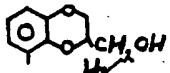
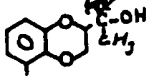
| Comp.No. | X | $(R_2)_n$ | $(R_2)_q$ | Salt | Melt.-point (°C) | Method of Ex. |
|---|---|---|---|---|---|---|
| 1 |  | H | H | HCl | 222-224 | I |
| 2 |  | H | H | HCl | 256-258 | I |
| 3 |  | H | H | HCl | 266-269 | I |
| 4 |  | Me | H | HCl | 220-224 | III |
| 5 |  | H | H | 2HCl | 228-233 | V |
| 6 |  | H | H | 2HCl | 226-230 | V |
| 7 |  | H | H | 2HCl | 236-240 | V |
| 8 |  | H | H | HCl | 186-189 | I |
| 9 |  | H | H | HCl | 179-181 | I |
| 10 |  | H | H | HCl | 228-235 | V |
| 11 |  | H | H | FUM. | 125 (decomp.) | V |
| 12 |  | H | H | HCl | 217-219 | II |
| 13 |  | H | H | HCl | 266 (decomp.) | II |
| 14 |  | H | H | HCl | 261-265 | I |
| 15 |  | H | H | HCl | 190-192 | I |

TABLE (cont.)

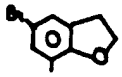
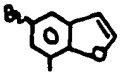
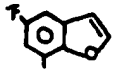
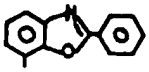
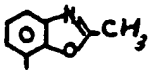
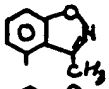
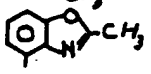
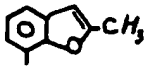
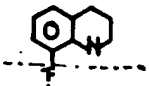
| Comp.No. | X | $(R_2)_n$ | $(R_2)_q$ | Salt | Melt.-point (°C) | Method of Ex. |
|---|---|---|---|---|---|---|
| 16 |  | H | H | 2HCl | 215-218 | I |
| 17 |  | H | H | HCl | 235-240 | I |
| 18 |  | H | H | HCl | 288-290 | I |
| 19 |  | H | H | 2HCl | 196-199 | I |
| 20 |  | H | H | HCl | 240-245 | I |
| 21 |  | H | H | HCl | 240 | II |
| 22 |  | H | H | 0.5 FUM. | 226-228 | I |
| 23 |  | H | H | FUM. | 195-196 | I |
| 24 |  | H | H | FUM. | 216-219 | VII |
| 25 |  | H | H | - | oil | I |
| 26 |  | H | H | HCl | 271-272 | IV |
| 27 |  | H | H | 2HCl | 216-222 | I |
| 28 |  | H | H | 2HCl | 330-334 | VI |
| 29 |  | H | H | 2.HCl | 215-221 | I |

TABLE (cont.)

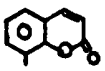
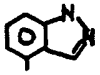
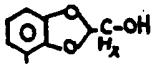
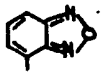
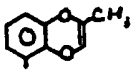
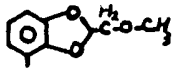
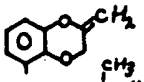
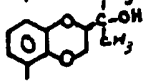
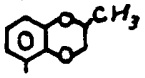
| Comp.No. | X | $(R_2)_n$ | $(R_2)_q$ | Salt | Melt.-point (°C) | Method of Ex. |
|---|---|---|---|---|---|---|
| 30 |  | Me(cis) | Me | HCl | 277-283 | III |
| 31 |  | H | H | HCl | 250 (dec.) | I |
| 32 |  | H | H | maleat | resin | II |
| 33 |  | H | H | 2.HCl | 195-197,5 | II |
| 34 |  | H | H | 2.HCl | 295-300 | VI |
| 35 |  | H | H | HCl | 250 (dec.) | IV |
| 36 |  | H | H | 2.HCl | 219-220 | II |
| 37 |  | H | H | FUM. | 208-211 | VI |
| 38 |  | H | H | 2.HCl | 190-193,5 | II |
| 39 |  | H | H | FUM. | 164-166 | II |
| 40 |  | H | H | 2.HCl | 216-218 | II |
| 41 |  | H | H | 2.HCl | 240-245 | VI |
| 42 |  | H | H | 2.HCl | 280-290 | V |
| 43 |  | H | H | 2.HCl | 257,5-265 | VI |
| 44 |  | H | H | 2.HCl | 276-280 | I |

TABLE (cont.)

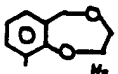
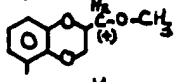
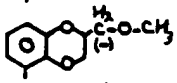
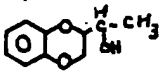
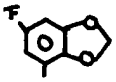
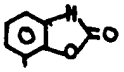
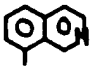
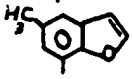
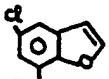
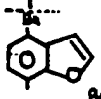
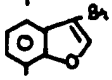
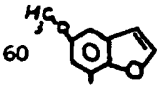
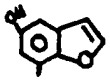
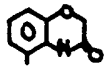
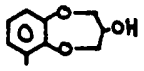
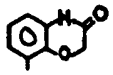
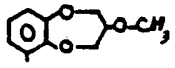
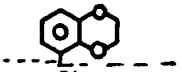
| Comp.No. | X | $(R_2)_n$ | $(R_2)_q$ | Salt | Melt.-point (°C) | Method of Ex. |
|---|---|---|---|---|---|---|
| 45 |  | H | H | 2.HCl | 207-212 | I |
| 46 |  | H | H | 2.HCl | 224 (dec.) | I |
| 47 |  | H | H | 2.HCl | 280-285 | II |
| 48 |  | H | H | 2.HCl | 195-197 | II |
| 49 |  | H | H | 2.HCl | 196-200 | II |
| 50 |  | H | H | 2.HCl | 263-265 | II |
| 51 |  | H | H | HCl | 228-229 | I |
| 52 |  | H | H | 2.HCl | 284-288 | VI |
| 53 |  | H | H | 2.HCl | 300 (dec.) | I |
| 54 |  | H | H | 2.HCl | 240 (dec.) | IV |
| 55 |  | H | H | HCl | 208-210 | I |
| 56 |  | H | H | HCl | 236-240 | I |
| 57 |  | H | H | HCl | 235,5-236 | VI |
| 58 |  | H | H | HCl | 228-234 | I |
| 59 |  | H | H | | resin | II |

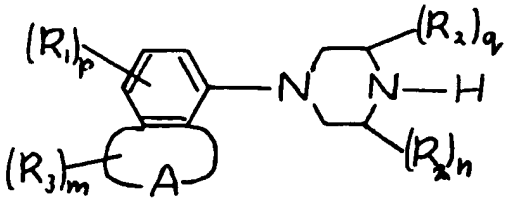
TABLE (cont.)

| Comp.No. | X | $(R_2)_n$ | $(R_2)_q$ | Salt | Melt.-point (°C) | Method of Ex. |
|---|---|---|---|---|---|---|
| 60 |  | H | H | 2.HCl | 186-190 | I |
| 61 |  | H | H | free base | 195-198 | VI |
| 62 |  | H | H | HCl | 310-330 | II |
| 63 |  | H | H | HCl | 200-205 | I |
| 64 |  | H | H | 2.HCl | 233 (dec.) | II |
| 65 |  | H | H | HCl | 290 (dec.) | I |
| 66 |  | H | H | 2.HCl | 200-202 | II |
| 67 |  | H | H | HCl | 285-286 | II |
| 68 |  | H | H | HCl | 330-331 | VI |
| 69 |  | Me(trans) | Me | HCl | 236-240 | III |
| 70 |  | H | H | HCl | 170-173 | I |
| 71 |  | H | H | HCl | 196-198 | I |
| 72 |  | H | H | HCl | 256-258 | I |

## Claims

**Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Pharmaceutical composition which comprises a piperazine derivative as the active substance, characterized in that as a psychotropically active substance it comprises at least one compound of general formula 1,



(1)

in which

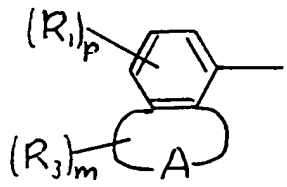
-$R_1$ is alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, alkylthio, nitro, amino, mono- or dialkylamino, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxyl, and p has the value 0-3;

-$R_2$ is an alkyl group and n and q can have the value 0 or 1;

-$R_3$ may have the same meanings as $R_1$, or is benzoyloxymethyl or methylidene, an oxo or thioxogroup, and m has the value 0-2;

-A forms, with the two carbon atoms of the phenyl group, saturated or fully or partly unsaturated cyclic group having 5-7 atoms in the ring, which comprises 1-3 hetero atoms from the group O, S and N, with the proviso that the sum of the number of oxygen and sulphur atoms is at most 2,

and exclusive of those compounds wherein n and q are 0, and A together with the two carbon atoms of the phenyl group forms a heterocyclic group having 5 of 6 ring atoms which as the only hetero atom contains a nitrogen atom on the meta position in relation to the piperazine group, and exclusive of compounds of general formula 1 wherein the group of general formula 2



(2)

is a 4- (or 7-) benzimidazolyl group which may be substituted in position 2 with alkyl, or a 7-indolyl group, or a 4- (or 7-) benzotriazolyl group, or a 5- (or 8-) carbo (or 3,4-dihydrocarbo)-styryl group, or a 8-quinolinyl group, or contains an acid addition salt or enantiomer there of.

2. A composition as claimed in Claim 1, characterized in that the active substance is
   a) 1-[5-(1,4-benzodioxanyl)] piperazine,
   b) 1-[8-(1,3-benzodioxanyl)] piperazine,
   c) 1-[7-(benzofuranyl)] piperazine,
   d) 1-[4-(1,3-benzodioxolyl)] piperazine,
   e) 1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine,
   f) 1-[7-(5-fluorobenzofuranyl)] piperazine,
   g) 1-[8-(1,2,3,4-tetrahydroquinolyl)]piperazine,
   h) 1-[8-(2-oxo-1-benzopyranyl)]piperazine,
   i) 1-[8-(2H-1-benzopyranyl)]piperazine,
   j) 1-[5-(2-methyl-1,4-benzodioxanyl)]piperazine,
   k) 1-[7-(4-fluorobenzofuranyl)]piperazine,
   l) 1-[8-(isoquinolyl)]piperazine,
   m) 1-[7-(4-bromobenzofuranyl)]piperazine,
   n) (+)-1-[5-(2-methoxymethyl-1,4-benzodioxanyl)]piperazine,
   o) 1-[7-(4-methylbenzofuranyl)]piperazine,
   p) 1-[7-(4-chlorobenzofuranyl)]piperazine,
   q) 1-[7-(5-chlorobenzofuranyl)]piperazine, or an acid addition salt thereof.

3. A method of preparing pharmaceutical compositions by bringing a pharmacologically active piperazine

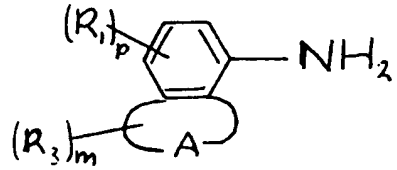
derivative into a form suitable for administration, characterized in that compositions with psychotropic activity are prepared by mixing a compound of general formula 1, in which $R_1$–$R_3$, A, p, n, q and m have the meanings given in Claim 1, or an acid addition salt or enantiomer thereof with solid or liquid carrier materials.

4. A method as claimed in Claim 3, characterized in that
a) 1-[5-(1,4-benzodioxanyl)] piperazine,
b) 1-[8-(1,3-benzodioxanyl)] piperazine,
c) 1-[7-(benzofuranyl)] piperazine,
d) 1-[4-(1,3-benzodioxolyl)] piperazine,
e) 1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine,
f) 1-[7-(5-fluorobenzofuranyl)] piperazine,
g) 1-[8-(1,2,3,4-tetrahydroquinolyl)]piperazine,
h) 1-[8-(2-oxo-1-benzopyranyl)]piperazine,
i) 1-[8-(2H-1-benzopyranyl)]piperazine,
j) 1-[5-(2-methyl-1,4-benzodioxanyl)]piperazine,
k) 1-[7-(4-fluorobenzofuranyl)]piperazine,
l) 1-[8-(isoquinolyl)]piperazine,
m) 1-[7-(4-bromobenzofuranyl)]piperazine,
n) (+)-1-[5-(2-methoxymethyl-1,4-benzodioxanyl)]piperazine,
o) 1-[7-(4-methylbenzofuranyl)]piperazine,
p) 1-[7-(4-chlorobenzofuranyl)]piperazine,
q) 1-[7-(5-chlorobenzofuranyl)]piperazine, or an acid addition salt thereof is used as the active substance.

5. Compounds of general formula 1 for use as an active psychotropic substance, in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, acid addition salts and enantiomers thereof.

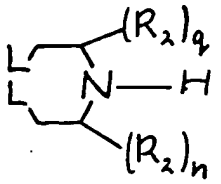
6. Compounds
a) 1-[5-(1,4-benzodioxanyl)] piperazine,
b) 1-[8-(1,3-benzodioxanyl)] piperazine,
c) 1-[7-(benzofuranyl)] piperazine,
d) 1-[4-(1,3-benzodioxolyl)] piperazine,
e) 1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine,
f) 1-[7-(5-fluorobenzofuranyl)] piperazine,
g) 1-[8-(1,2,3,4-tetrahydroquinolyl)]piperazine,
h) 1-[8-(2-oxo-1-benzopyranyl)]piperazine,
i) 1-[8-(2H-1-benzopyranyl)]piperazine,
j) 1-[5-(2-methyl-1,4-benzodioxanyl)]piperazine,
k) 1-[7-(4-fluorobenzofuranyl)]piperazine,
l) 1-[8-(isoquinolyl)]piperazine,
m) 1-[7-(4-bromobenzofuranyl)]piperazine,
n) (+)-1-[5-(2-methoxymethyl-1,4-benzodioxanyl)]piperazine,
o) 1-[7-(4-methylbenzofuranyl)]piperazine,
p) 1-[7-(4-chlorobenzofuranyl)]piperazine,
q) 1-[7-(5-chlorobenzofuranyl)]piperazine, and acid addition salts thereof.

7. A method of preparing piperazine derivatives of general formula 1 in a manner known for the synthesis of analogous compounds, characterized in that compounds as claimed in Claim 6 are prepared by:
a. converting a compound of general formula 3



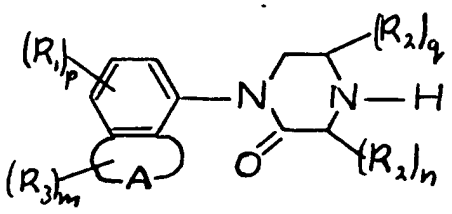

(3)

with a compound of general formula 4,



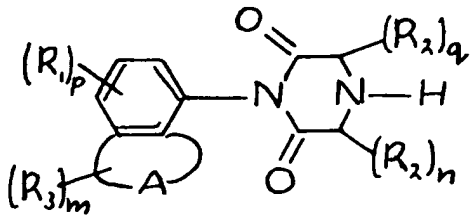
(4)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, and L is a leaving group; or
b. removing from a compound of general formula 1 in which the hydrogen atom at the N-atom is replaced by a protective group, said protective group, for example, by means of catalytic hydrogenation or acid hydrolysis, or
c. reducing a compound of general formula 5



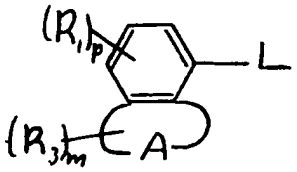
(5)

or general formula 6,



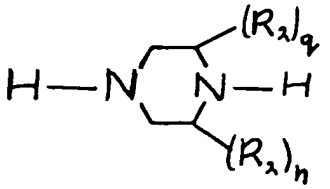
(6)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, or
d. converting a compound of general formula 7



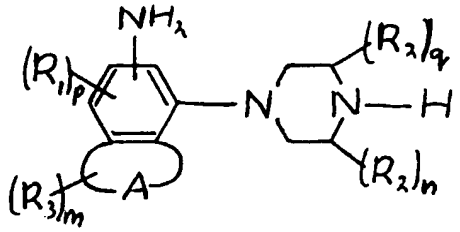
(7)

with a compound of general formula 8,



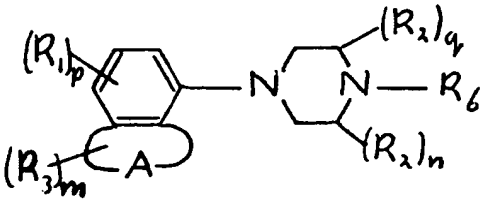
(8)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, and L is a leaving group, or
e. removing from a compound of general formula 9,



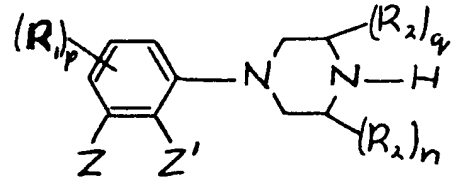
(9)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, the amino group, or
f. converting a compound of general formula 1 into another compound of general formula 1, for example, by hydrolizing an esterified hydroxyl function, or by introducing or saturating a double bond, or
g. converting a compound of the general formula 10



(10)

wherein A, $R_1$-$R_3$, m, n,p and q have the meaning given in Claim 1, and $R_6$ is an activating group, with a compound of the formula $R_2$-L, wherein $R_2$ has the above meaning and L is a leaving group, and removing the activating group $R_6$ in a way known per se, or
h. converting a compound of general formula 11,

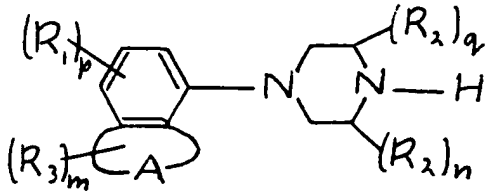


(11)

in which Z and Z', after cyclisation, lead to the desired group A, by means of a cyclisation reaction into a compound of general formula 1, in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1.

**Claims for the following Contracting State : AT**

1. A method of preparing pharmaceutical compositions by bringing a pharmacologically active piperazine derivative into a form suitable for administration, characterized in that compositions having psychotropic activity are prepared by mixing a compound of general formula 1,



(1)

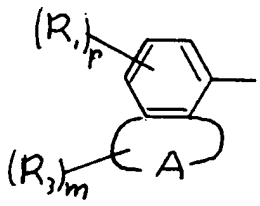
in which

-$R_1$ is alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, nitro, alkylthio, amino, mono- or dialkylamino, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxyl, and p has the value 0-3;

-$R_2$ is an alkyl group and n and q can have the value 0 or 1;

-$R_3$ may have the same meanings as $R_1$, or is benzoyloxymethyl or methylidene, an oxo or thioxogroup, and m has the value 0-2;

-A forms, with the two carbon atoms of the phenyl group, a saturated or fully or partly unsaturated cyclic group having 5-7 atoms in the ring, which comprises 1-3 hetero atoms from the group O, S and N, with the proviso that the sum of the number of oxygen and sulphur atoms is at most 2, and exclusive of those compounds wherein n and q are 0, and A together with the two carbon atoms of the phenyl group forms a heterocyclic group having 5 or 6 ring atoms which as the only hetero atom contains a nitrogen atom on the meta position in relation to the piperazine group, and exclusive of compounds of general formula 1, wherein the group of general formula 2



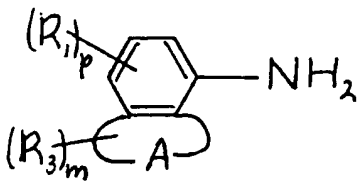
(2)

is a 4-(or 7-)benzimidazolyl group which may be substituted in position 2 with alkyl, or a 7-indolyl group, or a 4- (or 7-) benzotriazolyl group, or a 5-(or 8-) carbo (or 3,4-dihydrocarbo)-styryl group, or a 8-quinolinyl group, or an acid addition salt or enantiomer thereof with solid or liquid carrier materials.

2. A method as claimed in Claim 1, characterized in that
a) 1-[5-(1,4-benzodioxanyl)] piperazine,
b) 1-[8-(1,3-benzodioxanyl)] piperazine,
c) 1-[7-(benzofuranyl)] piperazine,
d) 1-[4-(1,3-benzodioxolyl)] piperazine,
e) 1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine,
f) 1-[7-(5-fluorobenzofuranyl)] piperzine,
g) 1-[8-(1,2,3,4-tetrahydroquinolyl)]piperazine,
h) 1-[8-(2-oxo-1-benzopyranyl)]piperazine,
i) 1-[8-(2H-1-benzopyranyl)piperazine,
j) 1-[5-(2-methyl-1,4-benzodioxanyl)]piperazine,
k) 1-[7-(4-fluorobenzofuranyl)]piperazine,
l) 1-[8-(isoquinolyl)]piperazine,
m) 1-[7-(4-bromobenzofuranyl)]piperazine,
n) (+)-1-[5-(2-methoxymethyl-1,4-benzodioxanyl)] piperazine
o) 1-[7-(4-methylbenzofurananyl)]piperazine, p) 1-[7-(4-chlorobenzofuranyl)]piperazine,
q) 1-[7-(5-chlorobenzofuranyl)]piperazine, or an acid addition salt thereof is used as the active substance.

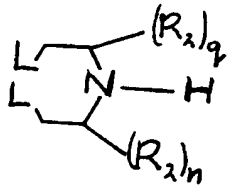
3. A method of preparing piperazine derivatives of general formula 1 in a manner known for the synthesis of analogous compounds, characterized in that compounds of general formula 1 in Claim 6 are prepared by:

a. converting a compound of general formula 3



(3)

with a compound of general formula 4,

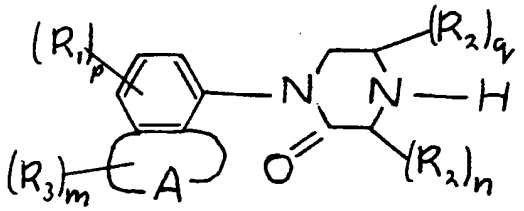


(4)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, and L is a leaving group; or

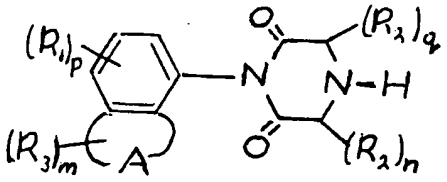
b. removing from a compound of general formula 1 in which the hydrogen atom at the N-atom is replaced by a protective group, said protective group, for example, by means of catalytic hydrogenation or acid hydrolysis, or

c. reducing a compound of general formula 5



(5)

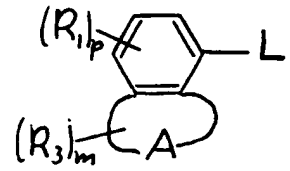
or general formula 6,



(6)

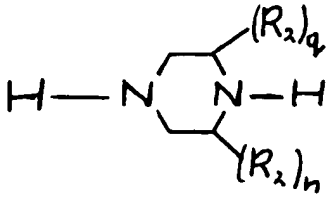
in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, or

d. converting a compound of general formula 7



(7)

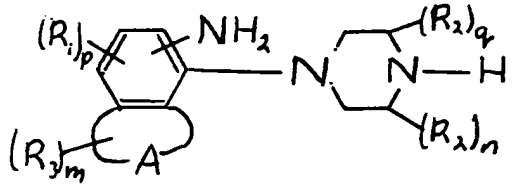
with a compound of general formula 8,



(8)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, and L is a leaving group, or

e. removing from a compound of general formula 9,

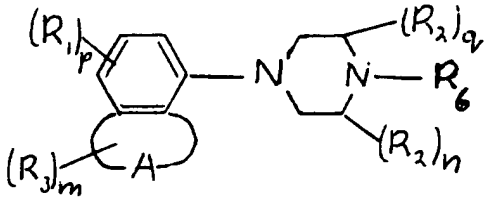


(9)

in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1, the amino group, or

f. converting a compound of general formula 1 into another compound of general formula 1, for example, by hydrolizing an esterified hydroxyl function, or by introducing or saturating a double bond, or

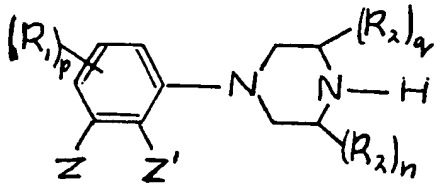
g. converting a compound of the general formula 10



(10)

wherein A, $R_1$-$R_3$, m, n, p and q have the meaning given in Claim 1, and $R_6$ is an activating group, with a compound of the formula $R_2$-L, wherein $R_2$ has the above meaning and L is a leaving group, and removing the activating group $R_6$ in a way known per se, or

h. converting a compound of general formula 11,



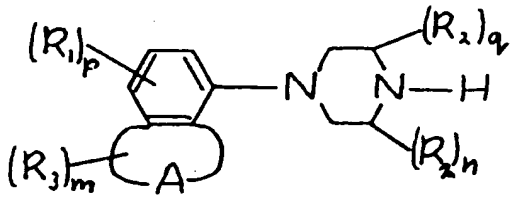
(11)

in which Z and Z', after cyclisation, lead to the desired group A, by means of a cyclisation reaction into a compound of general formula 1, in which $R_1$-$R_3$, A, p, n, q and m have the meanings given in Claim 1.

**Patentansprüche**

**Patentansprüche für folgende Verstragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Pharmazeutische Zusammensetzung, die ein Piperazinderivat als aktive Substanz enthält, dadurch gekennzeichnet, daß sie als psychotrop aktive Substanz mindestens eine Verbindung der allgemeinen Formel (1)



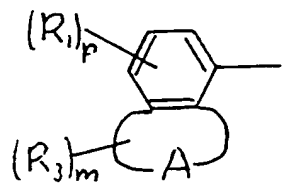
(1),

worin $R_1$ Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyalkyl, Alkoxy, Alkylthio, Nitro, Amino, Mono- oder Dialkylamino, Cyano, Halogen, Trifluormethyl, Trifluormethoxy oder Hydroxyl bedeutet und p den Wert Null bis 3 hat,

$R_2$ eine Alkylgruppe ist und n und q den Wert Null oder 1 haben können,

$R_3$ die gleichen Bedeutungen wie $R_1$ haben kann oder Benzoyloxymethyl oder Methyliden oder eine Oxo- oder Thioxogruppe ist und m den Wert Null bis 2 hat,

A mit den beiden Kohlenstoffatomen der Phenylgruppe eine gesättigte oder vollständig oder teilweise ungesättigte cyclische Gruppe mit 5 bis 7 Atomen im Ring bildet, die 1 bis 3 Heteroatome aus der Gruppe O, S und N aufweist, mit der Maßgabe, daß die Summe der Zahl von Sauerstoff- und Schwefelatomen höchstens 2 ist, und ausschließlich jener Verbindungen, worin n und q Null sind und A zusammen mit den beiden Kohlenstoffatomen der Phenylgruppe eine heterocyclische Gruppe mit 5 oder 6 Ringatomen bildet, die als einziges Heteroatom ein Stickstoffatom in m-Stellung in bezug auf die Piperazingruppe enthält, und ausschließlich Verbindungen der allgemeinen Formel (1), worin die Gruppe der allgemeinen Formel (2)



(2)

eine 4- (oder 7-)Benzimidazolylgruppe, die in Stellung 2 mit Alkyl substituiert sein kann, oder eine 7-Indolylgruppe oder eine 4- (oder 7-)Benzotriazolylgruppe oder eine 5- (oder 8-) Carbo- (oder 3,4-Dihydrocarbo)-styrylgruppe oder eine 8-Chinolinylgruppe ist, aufweist oder ein Säureadditionssalz oder Enantiomer hievon enthält.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die aktive Substanz

a) 1-[5-(1,4-Benzodioxanyl)]-piperazin,
b) 1-[8-(1,3-Benzodioxanyl)]-piperazin,
c) 1-[7-(Benzofuranyl)]-piperazin,
d) 1-[4-(1,3-Benzodioxolyl)]-piperazin,
e) 1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
f) 1-[7-(5-Fluorbenzofuranyl)]-piperazin,
g) 1-[8-(1,2,3,4-Tetrahydrochinolyl)]-piperazin,
h) 1-[8-(2-Oxo-1-benzopyranyl)]-piperazin,
i) 1-[8-(2H-1-Benzopyranyl)]-piperazin,
j) 1-[5-(2-Methyl-1,4-benzodioxanyl)]-piperazin,
k) 1-[7-(4-Fluorbenzofuranyl)]-piperazin,
l) 1-[8-(Isochinolyl)]-piperazin,
m) 1-[7-(4-Brombenzofuranyl)]-piperazin,
n) (+)-1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
o) 1-[7-(4-Methylbenzofuranyl)]-piperazin,
p) 1-[7-(4-Chlorbenzofuranyl)]-piperazin,
q) 1-[7-(5-Chlorbenzofuranyl)]-piperazin oder ein Säureadditionssalz hievon ist.

3. Verfahren zum Herstellen von pharmazeutischen Zusammensetzungen, indem ein pharmakologisch aktives Piperazinderivat in eine für Verabreichung geeignete Form gebracht wird, dadurch gekennzeichnet, daß Zusammensetzungen mit psychotroper Wirksamkeit durch Mischen einer Verbindung der allgemeinen Formel (1), worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Säureadditionssalzes oder Enantiomers hievon mit festen oder flüssigen Trägermaterialien hergestellt werden.

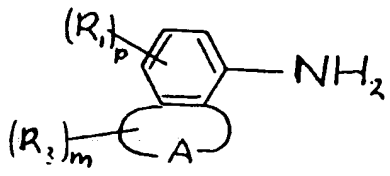
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß
a) 1-[5-(1,4-Benzodioxanyl)]-piperazin,
b) 1-[8-(1,3-Benzodioxanyl)]-piperazin,
c) 1-[7-(Benzofuranyl)]-piperazin,
d) 1-[4-(1,3-Benzodioxolyl)]-piperazin,
e) 1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
f) 1-[7-(5-Fluorbenzofuranyl)]-piperazin,
g) 1-[8-(1,2,3,4-Tetrahydrochinolyl)]-piperazin,
h) 1-[8-(2-Oxo-1-benzopyranyl)]-piperazin,
i) 1-[8-(2H-1-Benzopyranyl)]-piperazin,
j) 1-[5-(2-Methyl-1,4-benzodioxanyl)]-piperazin,
k) 1-[7-(4-Fluorbenzofuranyl)]-piperazin,
l) 1-[8-(Isochinolyl)]-piperazin,
m) 1-[7-(4-Brombenzofuranyl)]-piperazin,
n) (+)-1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
o) 1-[7-(4-Methylbenzofuranyl)]-piperazin,
p) 1-[7-(4-Chlorbenzofuranyl)]-piperazin,
q) 1-[7-(5-Chlorbenzofuranyl)]-piperazin oder ein Säureadditionssalz hievon als aktive Substanz verwendet wird.

5. Verbindungen der allgemeinen Formel (1) zur Verwendung als aktive psychotrope Substanz, worin $R_1$ bis $R_3$, A, p, n q und m die in Anspruch 1 angegebenen Bedeutungen haben, Säureadditionssalze und Enantiomere hievon.

6. Verbindungen
a) 1-[5-(1,4-Benzodioxanyl)]-piperazin,
b) 1-[8-(1,3-Benzodioxanyl)]-piperazin,
c) 1-[7-(Benzofuranyl)]-piperazin,
d) 1-[4-(1,3-Benzodioxolyl)]-piperazin,
e) 1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
f) 1-[7-(5-Fluorbenzofuranyl)]-piperazin,
g) 1-[8-(1,2,3,4-Tetrahydrochinolyl)]-piperazin,
h) 1-[8-(2-Oxo-1-benzopyranyl)]-piperazin,

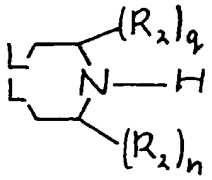
i) 1-[8-(2H-1-Benzopyranyl)]-piperazin,
j) 1-[5-(2-Methyl-1,4-benzodioxanyl)]-piperazin,
k) 1-[7-(4-Fluorbenzofuranyl)]-piperazin,
l) 1-[8-(Isochinolyl)]-piperazin,
m) 1-[7-(4-Brombenzofuranyl)]-piperazin,
n) (+)-1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
o) 1-[7-(4-Methylbenzofuranyl)]-piperazin,
p) 1-[7-(4-Chlorbenzofuranyl)]-piperazin,
q) 1-[7-(5-Chlorbenzofuranyl)]-piperazin und Säureadditionssalze hievon.

7. Verfahren zum Herstellen von Piperazinderivaten der allgemeinen Formel (1) auf eine für die Synthese analoger Verbindungen bekannte Weise, dadurch gekennzeichnet, daß Verbindungen, wie in Anspruch 6 beansprucht, hergestellt werden durch:
a. Umsetzen einer Verbindung der allgemeinen Formel (3)



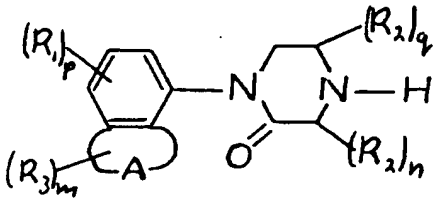
(3)

mit einer Verbindung der allgemeinen Formel (4)



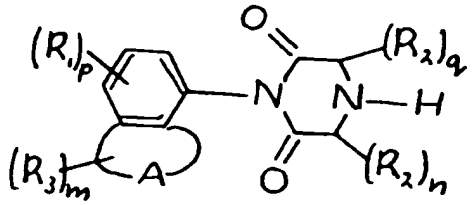
(4),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben und L eine Abgangsgruppe ist, oder
b. Entfernen der Schutzgruppe aus einer Verbindung der allgemeinen Formel (1), worin das Wasserstoffatom am N-Atom durch eine Schutzgruppe ersetzt ist, beispielsweise durch katalytische Hydrierung oder Säurehydrolyse, oder
c. Reduzieren einer Verbindung der allgemeinen Formel (5)



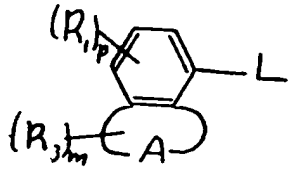
(5)

oder der allgemeinen Formel (6)



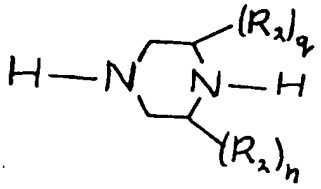
(6),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben, oder
d. Umsetzen einer Verbindung der allgemeinen Formel (7)



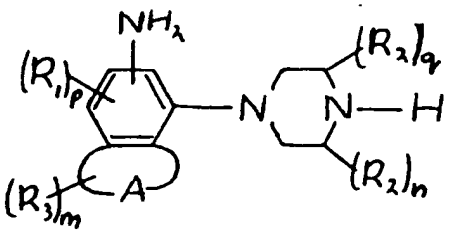
(7)

mit einer Verbindung der allgemeinen Formel (8)



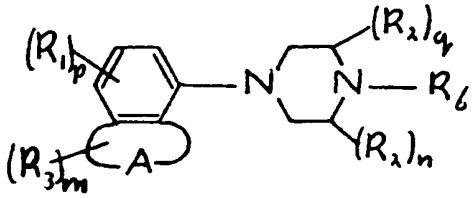
(8),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben und L eine Abgangsgruppe ist, oder
e. Entfernen der Aminogruppe aus einer Verbindung der allgemeinen Formel (9)



(9),

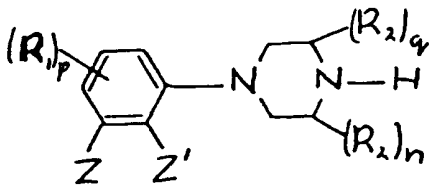
worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben, oder
f. Überführen einer Verbindung der allgemeinen Formel (1) in eine andere Verbindung der allgemeinen Formel (1), beispielsweise durch Hydrolysieren einer veresterten Hydroxylfunktion oder durch Einführen oder Sättigen einer Doppelbindung, oder
g. Umsetzen einer Verbindung der allgemeinen Formel (10)



(10),

worin A, $R_1$ bis $R_3$, m, n, p und q die in Anspruch 1 angegebenen Bedeutungen haben und $R_6$ eine aktivierende Gruppe ist, mit einer Verbindung der Formel $R_2$-L, worin $R_2$ die obige Bedeutung hat und L eine Abgangsgruppe ist, und Entfernen der aktivierenden Gruppe $R_6$ in an sich bekannter Weise, oder

h. Überführen einer Verbindung der allgemeinen Formel (11)

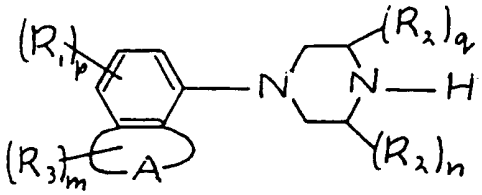


(11),

worin Z und Z' nach Cyclisierung zu der gewünschten Gruppe A führen, durch eine Cyclisierungsreaktion in eine Verbindung der allgemeinen Formel (1), worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben.

**Patentansprüche für folgenden Verstragsstaat : AT**

1. Verfahren zum Herstellen von pharmazeutischen Zusammensetzungen, indem ein pharmakologisch aktives Piperazinderivat in eine für Verabreichung geeignete Form gebracht wird, dadurch gekennzeichnet, daß Zusammensetzungen mit psychotroper Wirksamkeit durch Mischen einer Verbindung der allgemeinen Formel (1)



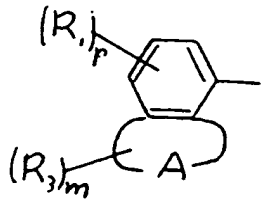
(1),

worin $R_1$ Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyalkyl, Alkoxy, Alkylthio, Nitro, Amino, Mono- oder Dialkylamino, Cyano, Halogen, Trifluormethyl, Trifluormethoxy oder Hydroxyl bedeutet und p den wert Null bis 3 hat,

$R_2$ eine Alkylgruppe ist und n und q den Wert Null oder 1 haben können,

$R_3$ die gleichen Bedeutungen wie $R_1$ haben kann oder Benzoyloxymethyl oder Methyliden oder eine Oxo- oder Thioxogruppe ist und m den Wert Null bis 2 hat,

A mit den beiden Kohlenstoffatomen der Phenylgruppe eine gesättigte oder vollständig oder teilweise ungesättigte cyclische Gruppe mit 5 bis 7 Atomen im Ring bildet, die 1 bis 3 Heteroatome aus der Gruppe O, S und N aufweist, mit der Maßgabe, daß die Summe der Zahl von Sauerstoff- und Schwefelatomen höchstens 2 ist, und ausschließlich jener Verbindungen, worin n und q Null sind und A zusammen mit den beiden Kohlenstoffatomen der Phenylgruppe eine heterocyclische Gruppe mit 5 oder 6 Ringatomen bildet, die als einziges Heteroatom ein Stickstoffatom in m-Stellung in bezug auf die Piperazingruppe enthält, und ausschließlich Verbindungen der allgemeinen Formel (1), worin die Gruppe der allgemeinen Formel (2)

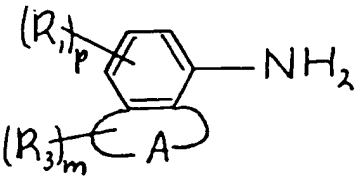


(2)

eine 4- (oder 7-)Benzimidazolylgruppe, die in Stellung 2 mit Alkyl substituiert sein kann, oder eine 7-Indolylgruppe oder eine 4- (oder 7-)Benzotriazolylgruppe oder eine 5- (oder 8-) Carbo- (oder 3,4-Dihydrocarbo)-styrylgruppe oder eine 8-Chinolinylgruppe ist, oder eines Säureadditionssalzes oder Enantiomers hievon mit festen oder flüssigen Trägermaterialien hergestellt werden.

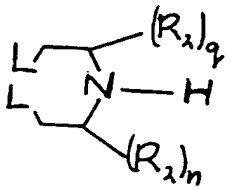
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß
   a) 1-[5-(1,4-Benzodioxanyl)]-piperazin,
   b) 1-[8-(1,3-Benzodioxanyl)]-piperazin,
   c) 1-[7-(Benzofuranyl)]-piperazin,
   d) 1-[4-(1,3-Benzodioxolyl)]-piperazin,
   e) 1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
   f) 1-[7-(5-Fluorbenzofuranyl)]-piperazin,
   g) 1-[8-(1,2,3,4-Tetrahydrochinolyl)]-piperazin,
   h) 1-[8-(2-Oxo-1-benzopyranyl)]-piperazin,
   i) 1-[8-(2H-1-Benzopyranyl)]-piperazin,
   j) 1-[5-(2-Methyl-1,4-benzodioxanyl)]-piperazin,
   k) 1-[7-(4-Fluorbenzofuranyl)]-piperazin,
   l) 1-[8-(Isochinolyl)]-piperazin,
   m) 1-[7-(4-Brombenzofuranyl)]-piperazin,
   n) (+)-1-[5-(2-Methoxymethyl-1,4-benzodioxanyl)]-piperazin,
   o) 1-[7-(4-Methylbenzofuranyl)]-piperazin,
   p) 1-[7-(4-Chlorbenzofuranyl)]-piperazin,
   q) 1-[7-(5-Chlorbenzofuranyl)]-piperazin oder ein Säureadditionssalz hievon als aktive Substanz verwendet wird.

3. Verfahren zum Herstellen von Piperazinderivaten der allgemeinen Formel (1) auf eine für die Synthese analoger Verbindungen bekannte Weise, dadurch gekennzeichnet, daß Verbindungen hergestellt werden durch:
   a. Umsetzen einer Verbindung der allgemeinen Formel (3)



(3)

mit einer Verbindung der allgemeinen Formel (4)

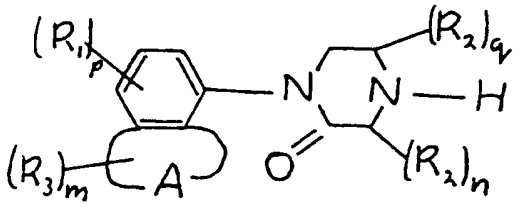


(4),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben und L eine Abgangsgruppe ist, oder

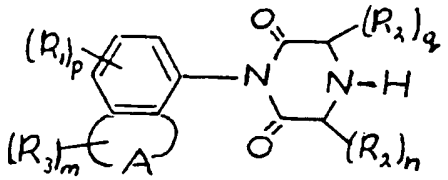
b. Entfernen der Schutzgruppe aus einer Verbindung der allgemeinen Formel (1), worin das Wasserstoffatom am N-Atom durch eine Schutzgruppe ersetzt ist, beispielsweise durch katalytische Hydrierung oder Säurehydrolyse, oder

c. Reduzieren einer Verbindung der allgemeinen Formel (5)



(5)

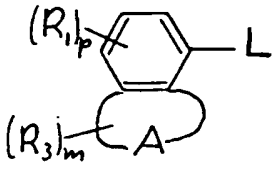
oder der allgemeinen Formel (6)



(6),

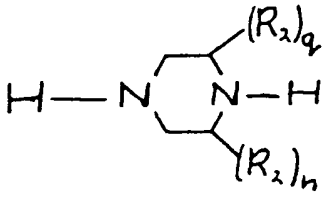
worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben, oder

d. Umsetzen einer Verbindung der allgemeinen Formel (7)



(7)

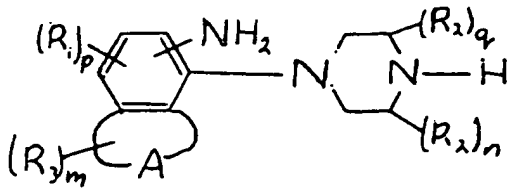
mit einer Verbindung der allgemeinen Formel (8)



(8),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben und L eine Abgangsgruppe ist, oder

e. Entfernen der Aminogruppe aus einer Verbindung der allgemeinen Formel (9)

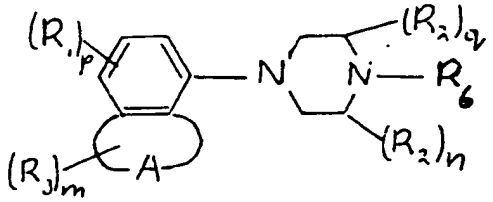


(9),

worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben, oder

f. Überführen einer Verbindung der allgemeinen Formel (1) in eine andere Verbindung der allgemeinen Formel (1), beispielsweise durch Hydrolysieren einer veresterten Hydroxylfunktion oder durch Einführen oder Sättigen einer Doppelbindung, oder

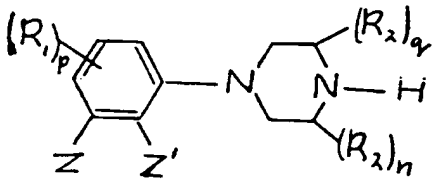
g. Umsetzen einer Verbindung der allgemeinen Formel (10)



(10),

worin A, $R_1$ bis $R_3$, m, n, p und q die in Anspruch 1 angegebenen Bedeutungen haben und $R_6$ eine aktivierende Gruppe ist, mit einer Verbindung der Formel $R_2$-L, worin $R_2$ die obige Bedeutung hat und L eine Abgangsgruppe ist, und Entfernen der aktivierenden Gruppe $R_6$ in an sich bekannter Weise, oder

h. Überführen einer Verbindung der allgemeinen Formel (11)



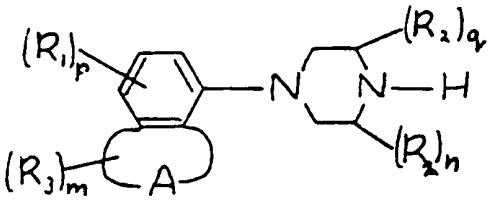
(11),

worin Z und Z' nach Cyclisierung zu der gewünschten Gruppe A führen, durch eine Cyclisierungsreaktion in eine Verbindung der allgemeinen Formel (1), worin $R_1$ bis $R_3$, A, p, n, q und m die in Anspruch 1 angegebenen Bedeutungen haben.

## Revendications

**Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Composition pharmaceutique, qui comprend un dérivé pipérazine comme substance active, caractérisée en ce que, comme substance à activité psychotrope, elle comprend au moins un composé de formule générale 1

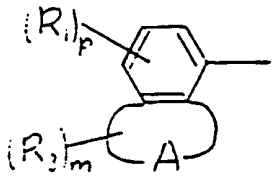


(1)

dans laquelle

- $-R_1$ est un groupe alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, alcoxy, alkylthio, nitro, amino, mono- ou dialkylamino, cyano, halogéno, trifluorométhyle, trifluorométhoxy, hydroxyle, et p a la valeur 0-3;
- $-R_2$ est un groupe alkyle et n et q peuvent avoir la valeur 0 ou 1;
- $-R_3$ peut avoir les mêmes significations que $R_1$, ou est un groupe benzoyloxyméthyle ou méthylidène, un groupe oxo ou thioxo, et m a la valeur 0-2;
- -A forme, avec les deux atomes de carbone du groupe phényle, un groupe cyclique saturé ou entièrement ou partiellement insaturé comportant 5-7 atomes dans le noyau, qui comprend 1-3 hétéroatomes du groupe O, S et N, à condition que la somme du nombre d'atomes d'oxygène et d'atomes de soufre soit d'au plus 2,

et à l'exclusion des composés dans lesquels n et q sont nuls et A forme, avec les deux atomes de carbone du groupe phényle, un groupe hétérocyclique comportant 5 ou 6 atomes dans le noyau qui contient, comme seul hétéroatome, un atome d'azote en position méta par rapport au groupe pipérazine, et à l'exclusion des composés de formule générale 1 dans lesquels le groupe de formule générale 2



(2)

est un groupe 4- (ou 7-) benzimidazolyle, qui peut être substitué en position 2 par un groupe alkyle, ou un groupe 7-indolyle, ou un groupe 4- (ou 7-) benzotriazolyle, ou un groupe 5- (ou 8-) carbo (ou 3,4-dihydrocarbo) styryle, ou un groupe 8-quinoléinyle, ou contient un sel d'addition avec un acide ou un énantiomère de celui-ci.

2. Composition selon la revendication 1, caractérisée en ce que la substance active est
   a) la 1-[5-(1,4-benzodioxanyl)]pipérazine,
   b) la 1-[8-(1,3-benzodioxanyl)]pipérazine,
   c) la 1-[7-(benzofurannyl)]pipérazine,
   d) la 1-[4-(1,3-benzodioxolyl)]pipérazine,
   e) la 1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
   f) la 1-[7-(5-fluorobenzofurannyl)]pipérazine,
   g) la 1-[8-(1,2,3,4-tétrahydroquinoléyl)]pipérazine,
   h) la 1-[8-(2-oxo-1-benzopyranyl)]pipérazine,
   i) la 1-[8-(2-H-1-benzopyranyl)]pipérazine,
   j) la 1-[5-(2-méthyl-1,4-benzodioxanyl)]pipérazine,
   k) la 1-[7-(4-fluorobenzofurannyl)]pipérazine,
   l) la 1-(8-(isoquinoléyl)]pipérazine,
   m) la 1-[7-(4-bromobenzofurannyl)]pipérazine,
   n) la (+)-1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
   o) la 1-[7-(4-méthylbenzofurannyl)]pipérazine,
   p) la 1-[7-(4-chlorobenzofurannyl)]pipérazine,
   q) la 1-[7-(5-chlorobenzofurannyl)]pipérazine, ou un de leurs sels d'addition avec un acide.

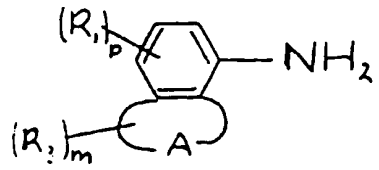
3. Procédé de préparation de compositions pharmaceutiques, qui consiste à mettre un dérivé pipérazine à activité pharmacologique sous une forme convenant à l'administration, caractérisé en ce que des compositions à activité psychotrope sont préparées par mélange d'un composé de formule générale 1, dans laquelle $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, ou d'un de ses sels d'addition avec un acide ou énantiomères, avec des véhicules solides ou liquides.

4. Procédé selon la revendication 3, caractérisé en ce que l'on utilise, comme substance active,
a) la 1-[5-(1,4-benzodioxanyl)]pipérazine,
b) la 1-[8-(1,3-benzodioxanyl)]pipérazine,
c) la 1-[7-(benzofurannyl)]pipérazine,
d) la 1-[4-(1,3-benzodioxolyl)]pipérazine,
e) la 1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
f) la 1-[7-(5-fluorobenzofurannyl)]pipérazine,
g) la 1-[8-(1,2,3,4-tétrahydroquinoléyl)]pipérazine,
h) la 1-[8-(2-oxo-1-benzopyranyl)]pipérazine,
i) la 1-[8-(2-H-1-benzopyranyl)]pipérazine,
j) la 1-[5-(2-méthyl-1,4-benzodioxanyl)]pipérazine,
k) la 1-[7-(4-fluorobenzofurannyl)]pipérazine,
l) la 1-[8-(isoquinoléyl)]pipérazine,
m) la 1-[7-(4-bromobenzofurannyl)]pipérazine,
n) la (+)-1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
o) la 1-[7-(4-méthylbenzofurannyl)]pipérazine,
p) la 1-[7-(4-chlorobenzofurannyl))pipérazine,
q) la 1-[7-(5-chlorobenzofurannyl)]pipérazine, ou un de leurs sels d'addition avec un acide.

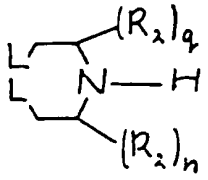
5. Composés de formule générale 1 à utiliser comme substances psychotropes actives, dans lesquels $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, ou un de leurs sels d'addition avec un acide ou énantiomères.

6. Composés
a) la 1-[5-(1,4-benzodioxanyl)]pipérazine,
b) la 1-[8-(1,3-benzodioxanyl)]pipérazine,
c) la 1-[7-(benzofurannyl)]pipérazine,
d) la 1-[4-(1,3-benzodioxolyl)]pipérazine,
e) la 1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
f) la 1-[7-(5-fluorobenzofurannyl)]pipérazine,
g) la 1-[8-(1,2,3,4-tétrahydroquinoléyl)]pipérazine,
h) la 1-[8-(2-oxo-1-benzopyranyl)]pipérazine,
i) la 1-[8-(2-H-1-benzopyranyl)[pipérazine,
j) la 1-[5-(2-méthyl-1,4-benzodioxanyl)]pipérazine,
k) la 1-[7-(4-fluorobenzofurannyl)]pipérazine,
l) la 1-[8-(isoquinoléyl))pipérazine,
m) la 1-[7-(4-bromobenzofurannyl)]pipérazine,
n) la (+)-1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
o) la 1-[7-(4-méthylbenzofurannyl)]pipérazine,
p) la 1-[7-(4-chlorobenzofurannyl)]pipérazine,
q) la 1-[7-(5-chlorobenzofurannyl)]pipérazine, et leurs sels d'addition avec un acide.

7. Procédé de préparation de dérivés pipérazines de formule générale 1, d'une manière connue pour la synthèse de composés analogues, caractérisé en ce que l'on prépare des composés selon la revendication 6 :
a. en transformant un composé de formule générale 3



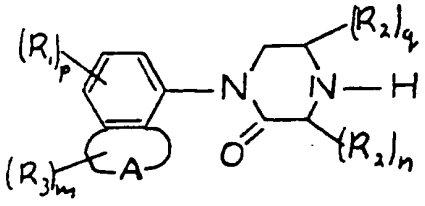
avec un composé de formule générale 4



dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, et L est un groupe partant; ou

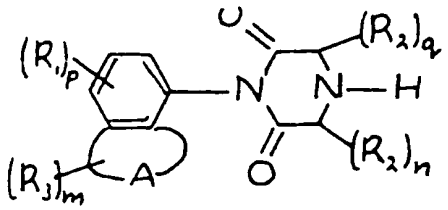
b. en éliminant, d'un composé de formule générale 1, dans lequel l'atome d'hydrogène fixé sur l'atome de N est remplacé par un groupe protecteur, ledit groupe protecteur, par exemple au moyen d'une hydrogénation catalytique ou d'une hydrolyse acide, ou

c. en réduisant un composé de formule générale 5



(5)

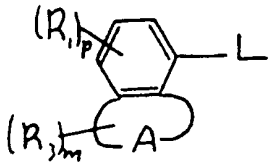
ou de formule générale 6



(6)

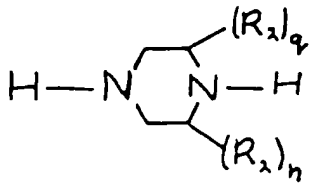
dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, ou

d. en transformant un composé de formule générale 7



(7)

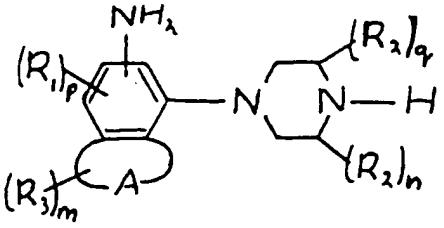
avec un composé de formule générale 8



(8)

dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, et L est un groupe partant, ou

e. en éliminant, d'un composé de formule générale 9

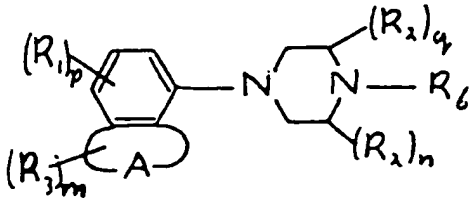


(9)

dans laquelle $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, le groupe amino, ou

f. en transformant un composé de formule générale 1 en un autre composé de formule générale 1, par exemple en hydrolysant une fonction hydroxyle estérifiée, ou en introduisant ou en saturant une double liaison, ou

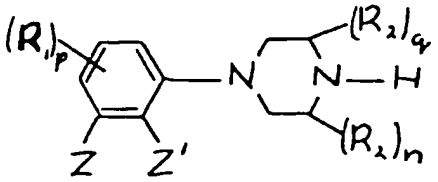
g. en transformant un composé de formule générale 10



(10)

dans laquelle A, $R_1$-$R_3$, m, n, p et q ont les significations données dans la revendication 1, et $R_6$ est un groupe activant, avec un composé de formule $R_2$-L, dans laquelle $R_2$ a la même signification que ci-dessus et L est un groupe partant, et en éliminant le groupe activant $R_6$ d'une manière connue en soi, ou

h. en transformant un composé de formule générale 11

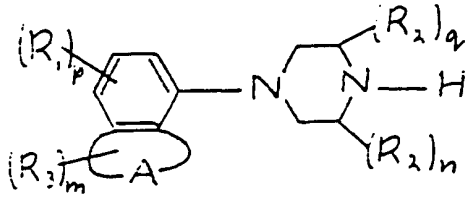


(11)

dans laquelle Z et Z', après cyclisation, conduisent au groupe A recherché, au moyen d'une réaction de cyclisation, en un composé de formule générale 1, dans laquelle $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1.

**Revendications pour l'Etat contractant suivant : AT**

1. Procédé de préparation de compositions pharmaceutiques, qui consiste à amener un dérivé pipérazine pharmacologiquement actif sous une forme convenant à l'administration, caractérisé en ce que l'on prépare des compositions ayant une activité psychotrope en mélangeant un composé de formule générale 1



(1)

dans laquelle

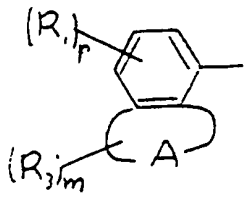
-$R_1$ est un groupe alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, alcoxy, nitro, alkylthio, amino, mono- ou dialkylamino, cyano, halogéno, trifluorométhyle, trifluorométhoxy, hydroxyle, et p a la valeur 0-3;

-$R_2$ est un groupe alkyle et n et q peuvent avoir la valeur 0 ou 1;

-$R_3$ peut avoir les mêmes significations que $R_1$, ou est un groupe benzoyloxyméthyle ou méthylidène, un groupe oxo ou thioxo, et m a la valeur 0-2;

-A forme, avec les deux atomes de carbone du groupe phényle, un groupe cyclique saturé ou entièrement ou partiellement insaturé comportant 5-7 atomes dans le noyau, qui comprend 1-3 hétéroatomes du groupe O, S et N, à condition que la somme du nombre d'atomes d'oxygène et d'atomes de soufre soit d'au plus 2,

et à l'exclusion des composés dans lesquels n et q sont nuls et A forme, avec les deux atomes de carbone du groupe phényle, un groupe hétérocyclique comportant 5 ou 6 atomes dans le noyau qui contient, comme seul hétéroatome, un atome d'azote en position méta par rapport au groupe pipérazine, et à l'exclusion des composés de formule générale 1 dans lesquels le groupe de formule générale 2



(2)

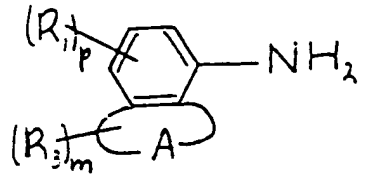
est un groupe 4- (ou 7-) benzimidazolyle, qui peut être substitué en position 2 par un groupe alkyle, ou un groupe 7-indolyle, ou un groupe 4- (ou 7-) benzotriazolyle, ou un groupe 5- (ou 8-) carbo (ou 3,4-dihydrocarbo) styryle, ou un groupe 8-quinoléinyle, ou un sel d'addition avec un acide ou un énantiomère de celui-ci, avec des véhicules solides ou liquides.

2. Procédé selon la revendication 1, caractérisé en ce que l'on utilise, comme substance active,
   a) la 1-[5-(1,4-benzodioxanyl)]pipérazine,
   b) la 1-[8-(1,3-benzodioxanyl)]pipérazine,
   c) la 1-[7-(benzofurannyl)]pipérazine,
   d) la 1-[4-(1,3-benzodioxolyl)]pipérazine,
   e) la 1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
   f) la 1-[7-(5-fluorobenzofurannyl)]pipérazine,
   g) la 1-[8-(1,2,3,4-tétrahydroquinoléyl)]pipérazine,
   h) la 1-[8-(2-oxo-1-benzopyranyl)]pipérazine,
   i) la 1-[8-(2-H-1-benzopyranyl)]pipérazine,
   j) la 1-[5-(2-méthyl-1,4-benzodioxanyl)]pipérazine,
   k) la 1-[7-(4-fluorobenzofurannyl)]pipérazine,
   l) la 1-[8-(isoquinoléyl)]pipérazine,

m) la 1-[7-(4-bromobenzofurannyl)]pipérazine,
n) la (+)-1-[5-(2-méthoxyméthyl-1,4-benzodioxanyl)]pipérazine,
o) la 1-[7-(4-méthylbenzofurannyl)]pipérazine,
p) la 1-[7-(4-chlorobenzofurannyl)]pipérazine,
q) la 1-[7-(5-chlorobenzofurannyl)]pipérazine, ou ou un de ses sels d'addition avec un acide.

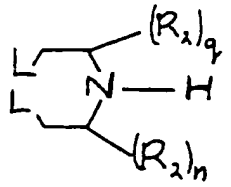
3. Procédé de préparation de dérivés pipérazines de formule générale 1, d'une manière connue pour la synthèse de composés analogues, caractérisé en ce que l'on prépare des composés de formule générale 1 selon la revendication 1 :

a. en transformant un composé de formule générale 3



(3)

avec un composé de formule générale 4

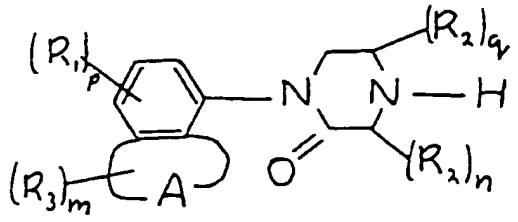


(4)

dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, et L est un groupe partant; ou

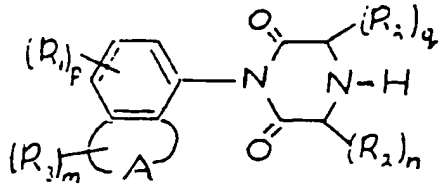
b. en éliminant, d'un composé de formule générale 1, dans lequel l'atome d'hydrogène fixé sur l'atome de N est remplacé par un groupe protecteur, ledit groupe protecteur, par exemple au moyen d'une hydrogénation catalytique ou d'une hydrolyse acide, ou

c. en réduisant un composé de formule générale 5



(5)

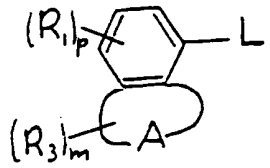
ou de formule générale 6



(6)

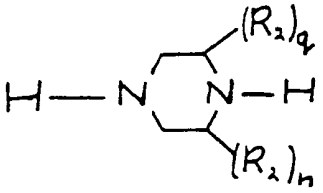
dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, ou

d. en transformant un composé de formule générale 7



(7)

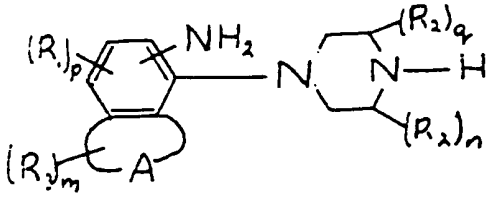
avec un composé de formule générale 8



(8)

dans lesquelles $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, et L est un groupe partant, ou

e. en éliminant, d'un composé de formule générale 9

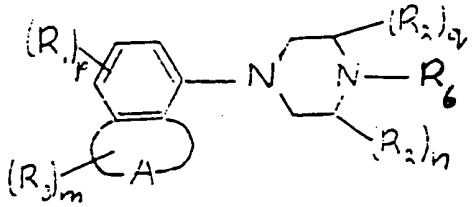


(9)

dans laquelle $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1, le groupe amino, ou

f. en transformant un composé de formule générale 1 en un autre composé de formule générale 1, par exemple en hydrolysant une fonction hydroxyle estérifiée, ou en introduisant ou en saturant une double liaison, ou

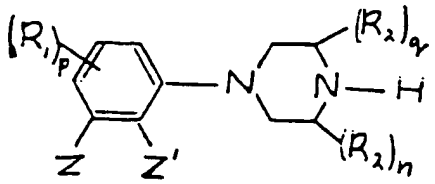
g. en transformant un composé de formule générale 10



(10)

dans laquelle A, $R_1$-$R_3$, m, n, p et q ont les significations données dans la revendication 1, et $R_6$ est un groupe activant, avec un composé de formule $R_2$-L, dans laquelle $R_2$ a la même signification que ci-dessus et L est un groupe partant, et en éliminant le groupe activant $R_6$ d'une manière connue en soi, ou

h. en transformant un composé de formule générale 11



(11)

dans laquelle Z et Z', après cyclisation, conduisent au groupe A recherché, au moyen d'une réaction de cyclisation, en un composé de formule générale 1, dans laquelle $R_1$-$R_3$, A, p, n, q et m ont les significations données dans la revendication 1.